THE RHODE ISLAND MEDICAL JOURNAL

Owned and Published by the Rhode Island Medical Society. Issued Monthly

VOLUME XIII No. 4 | Whole No. 247 | PROVIDENCE, R. I., APRIL, 1930 | PER YEAR $2.00 SINGLE COPY 25 CENTS

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ENTERED AS SECOND-CLASS MATTER AT THE POST OFFICE AT PROVIDENCE, R. I., UNDER ACT OF MARCH 3, 1879

THE RHODE ISLAND MEDICAL JOURNAL

The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee

VOLUME XIII
NUMBER 4
Whole No 247
PROVIDENCE, R. I., APRIL, 1930
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ORIGINAL ARTICLES

ORGANOTHERAPY IN GYNECOLOGY*

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Mr. President and Members of the Providence Medical Association:

I am not here tonight to prove to you by report of personal cases, or experimental studies, the value or otherwise of the commercial preparations of internal secretion in treating gynecological conditions.

If I felt that the future for glandular therapy in gynecology showed no more promise than past clinical experience with the various commercial preparations would justify us in expecting, I would be more than reluctant in appearing before you and taking up your valuable time. My own experience with the commercial products in treating the various gynecological conditions has always been very unsatisfactory. I have never seen a gynecological case where I could justly attribute improvement to ovarian or other glandular therapy alone. I know that there are some among you who may be of different mind. I welcome your helpful criticism.

Let us first consider what the history of glandular therapy in general and ovarian therapy in particular has been, and try to learn the reasons why ovarian therapy has failed so signally in the past, and what developments seem to justify our hopes for better things in the future.

Some knowledge of the diseases due to endocrine failure had been accumulating since 1825, when Parry described exophthalmic goitre—Addison described tuberculosis of the adrenals in 1855—Berthold transplanted testes of cocks and demonstrated internal secretion of testes in 1849—Koch and Reverdin in 1882, described athyreosis—Murray in 1892, gave fresh or glycerine extract of thyroid gland to a woman with myxedema and kept her in excellent health thirty-four years.

"This striking result was followed immediately by a furore over gland therapy and every imaginable gland or body tissue was prescribed with total failure. Although the early enthusiasm led to ill balanced haste in endocrine therapy, the clinical study of endocrinology has progressed steadily and has now reached a considerable degree of perfection." (Frank: *American Journal Obstetrics and Gynecology,* January, 1928.)

As in other fields of therapy where the clinician has made the first discovery, the laboratory worker has come in with trained scientific mind and method, detached from the necessity of the patient, free from crowding cares and anxious hopes, with no axe to grind, and with infinite pains and carefully controlled observations over a period of years has built up a mass of knowledge which is now breaking through the hodge podge of empiricism and widely conflicting clinical opinion, and placing organotherapy on a sound scientific basis.

The thyroid, parethyroid, adrenal, posterior pituitary and pancreatic (insulin) hormone have been isolated and are now acknowledged agents beyond question of doubt demonstrated by carefully controlled objective pharmocologic and physiologic criteria and proofs. Frank states ("Endocrin Therapy," *A. J. & O. G.,* January, 1928). "Each advance has been based upon the discovery or elaboration of some specific and pathognomonic test for a given product." The thyroid by the effect of its administration on metabolism, the parethyroid by its effect on calcium-metabolism and in controlling tetany in animals where the parethyroid has been removed, the adrenal by its effect in raising blood pressure, insulin by its quantitative effect on blood sugar level, the posterior pituitary by its effect on smooth muscle. Until such a test is found scientific study cannot advance. This explains why the study of the sex homone had not progressed beyond the early stage of knowing that castration causes atrophy of the genitals and that

*Read before the Medical Association, November 4th, 1929.

transplantation prevents such atrophy in castrated animals. Graves in the third edition of his text book, 1923, states, "It has been justly asserted that most of the work thus far done on ovarian therapy has been unscientific in character and that the clinical results from its use which have been reported are therefore in large part untrustworthy." He ascribes the lack of progress to certain impeding factors which serve as a serious handicap to proper scientific investigation: (1) Vagueness of knowledge of physiologic processes of pelvic organs where the homone originates; (2) impossibility of making standard tests for most clinical reactions for which administered; (3) animal experiments useless on account of exclusively human nature of reactions; (4) nature of secretion not known —no standardization—i. e., no pathognomonic test showing its presence or absence in a given preparation. Thus the clinicians were struggling along using commercial preparations on purely empirical grounds, having no or little exact knowledge of the physiological functions of the ovary, using different preparations whose potency or even content of sex homone was undeterminable, some using corpus luteum extracts, some whole ovary, some ovarian residue, with results that were negative or contradictory. Ovarian therapy was awaiting a fuller understanding of the female physiology and a method of testing for the presence or absence of the homone.

The anatomist and physiologist had however, been quietly working along and in 1917, Stockard and Papanicolaon in their studies on the oestrous cycle of the guinea pig worked out a method whereby the ovarian cycle could be accurately followed by means of observing the vaginal spread or smear microscopically. They found that the different periods, the diestral or quiescent, the proestral and oestral periods were represented by definite stages of follicular development which had a corresponding stage of development in the uterus, tubes and vaginal tract that the vaginal spreads of the diestrum, piestrum and oestrum are characteristic for their respective periods.

E. Allen in 1922, described the oestrus cycle for the mouse. Allen's work is of great importance in the advance of our knowledge because it furnishes the basis for the biological test for sex hormone at present used. The mouse furnishes the best laboratory animal for this test because its oestrous cycle is of short duration (48 hours) and because the changes are clear cut and definite and the animal itself inexpensive and easy to handle.

In 1917, Frank showed that undiluted follicle fluid produced marked hyperplasia of the uterus vagina and breasts in virgin immature rabbits and drew the warranted deduction that the sexual cycle is initiated and due to ovarian follicular action. Like results were obtained with corpus luteum and placenta extracts and led Frank to the belief that the ovum was the chief factor and that the stages in its development, primordial follicle, graafian follicle, corpus luteum and placenta, constituted together the "gestational gland."

Allen and Doisy (Sept. 8, 1923, *J. A. M. A.*) using spayed mice showed that follicular fluid injected subcutaneously will produce all the phenomena of oestrus, including the characteristic changes in the vaginal smear, the hypertrophy of the tubular tract and the breasts and the desire for and acceptance of the male. They used the follicular fluid from the ovary of the sow, which they aspirated through a needle and injected at first as a whole. When the characteristic changes appeared, they further purified the fluid by filtering through a Berkefeldt filter and found that the filtrate was the active portion, and not the cellular contents of the fluids. The fluid was then treated to rid it of protein substances and the remaining solution was still potent. This hormone containing fluid was now injected into other ovarectimized animals and all the phenomena of heat occurred. They draw from their experiments certain conclusions. (1) The follicular hormone acts as an efficient sustitute for the ovary in producing the oestral cycle. (2) It is capable of producing typical mating instincts in spayed animals. (3) It will produce sexual maturity if injected in animals immediately after weaning. (4) Commercial preparations tested by the vaginal spread method are negative. Preparations of whole ovary corpus luteum and ovarian residue manufactured by the large commercial houses are inert in their power to produce oestrus in spayed animals. (5) The hormone is not species specific, i. e., the hormone recovered from the pig is efficient for all animals tested.

Following the perfection of this method and the demonstration of the hormone much work

has been done. The various tissues of animals and the human have been carefully examined. The hormone has been found in the corpus luteum, the placenta, the fetal membranes, the amniotic fluid and the urine and the cirulating blood. Frank has perfected a method of estimating its quantity in the circulating blood and is engaged in interesting studies as to its concentration during the menstrual stages in abnormal and normal conditions with some conclusions. (1) The concentration increases from tenth day after preceding menstruation up to menstruation. (2) With onset of mentruation or of pregnancy the hormone disappears. (3) It is found in great concentration in menstrual and post partum blood. (4) It is found in circulating blood after the twelfth week of pregnancy. (5) Functional bleeding cases show excessive hormone in the circulating blood. (6) Functional overactivity may be demonstrated even in amenorrheas. (7) Other interesting facts have been observed concerning sex determination, sterility, etc., which time does not allow me to further consider. Thus a new field for scientific study of pelvic physiology and functional pathology is open which promises bright things for the future. As yet the results in the human with the new hormone have not come up to expectation. The reactions of the human female to injection of the hormone are not accurate and clear cut as in the lower forms. This may be due to the fact that as yet a potent enough, sufficiently concentrated preparation, is not available. Again, as is believed by Loeb, Papanicolan and Smith and Novak, there may be an important hormone of the corpus luteum in woman not present in lower animals antagonistic to the follicular hormone, and to get the proper effect these hormones may have to be adminstered in proper sequence. A potent preparation of corpus luteum is yet to be found.

Recent investigations have shown that anterior pituitary implants have a profound stimulative effect on ovarian function, causing premature maturity with hypertrophy of ovary, rapid growth of follicles and of secondary sexual characteristics. No effect is observed, however, in spayed animals showing that the effect is stimulative to ovaries and not direct. Further work along this line, particularly in isolating the hormone of the anterior pituitary, may lead to development of method of applying therapeutically. The work of Smith and Engle indicated that anterior pituitary by mouth is worthless.

There is so much interesting work being done in this field that one is tempted to go on indefinitely, but I must conclude. The future of ovarian therapy lies in carefully checked scientific study, calling for team work between the anatomist, the physiologist, the biochemist and the clinical observer. The age of the empiricist has gone. There are yet difficult problems to solve but they are most interesting ones and the ground work has been done. Few of us are in a position to take active part in this work, but if I have stimulated your interest to follow this work in your reading I shall feel that my time has been well spent. I refer you particularly to the writings of Allen and his co-workers; and to the work of Robert T. Frank of New York, and Emil Novak of Baltimore.

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A CASE OF MYASTHENIA GRAVIS WITH CERTAIN UNUSUAL FEATURES*

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In 1878, Erb, at the Congress of Medicine at Wiesbaden, in what has been described as a masterly description, presented three cases characterized by disturbance of the cranial and upper cervical nerves, with, in particular, a double ptosis, an inconstant paresis of the external muscles of the eye, weakness of the muscles of mastication and of the muscles of the neck. In addition to these essential symptoms were disturbances of deglutition and weakness of the extremities. The clinical picture, he said, suggested bulbar palsy, but possessed important differences. This was the first description of what is now known as myasthenia gravis. In 1893, Goldflam added to the description another characteristic symptom, that of fatigability. Because of the contributions of these two men the disease is sometimes known, particularly by the French, as the Erb-Goldflam disease.

The exact place of myasthenia gravis in general pathology is uncertain. Some writers place it among diseases of the muscles, others describe it as a disease of the nerves, others place it among disturbances of the endocrine glands or again in the group of disorders of the neuro-vegetative system. As each of these particular fields has its own methods of investigation, different factors have been stressed with a resulting lack of synthesis. Usually, however, it has been looked upon as a disease of the nervous system and therefore studied by clinical and anatomical methods.

As to etiology, infections may undoubtedly serve as a predisposing cause. Pregnancy is always mentioned as a possible etiological factor. Patients suffering from the disease are many times anemic and of asthenic constitution. A hereditary character has not been mentioned except in one case reported by Marinesco. This fact is of interest in view of the familial history of the disease in the patient I am now presenting. The disease occurs more often in women and the usual age is between twenty and fifty but Mailhouse reported a case in a child of two and one-half, and Keschner one at fifty-nine.

Perhaps as clinicians we shall more easily orient ourselves if we discuss the symptoms before we consider anatomical changes or the more recent theories as to its pathogenesis.

It is convenient to classify the symptoms under six categories:

1. Fatigue.
2. Ocular disturbances.
3. Disturbances of facial expression, phonation and deglutition.
4. Other neuro-muscular disorders.
5. Disorders of viscera and body fluids.
6. Endocrine and sympathetic disturbances.

1. Fatigue. Goldflam first recognized that the essential motor symptom was a fatigability rather than a true paralysis. In the beginning of the disease we find neither paralysis nor paresis but a characteristic fatigability of certain muscles with a gradual loss of their energy with repeated efforts and a rapid return to their normal state after a brief period of rest. The muscles of which the patient makes most use are often the ones first affected. The fatigue is variable; it appears and disappears without apparent cause. It is more marked in the evening. It is usually limited to muscle groups put into activity during the execution of a voluntary act, but sometimes appears in a neighboring group or a set considerably removed from the ones exercised.

The degree of muscular exhaustion may be objectively shown by ergographic curves which show that the muscle contractions obtained during the first movement have a normal amplitude, but if the movements follow with a rather rapid rhythm the force of the contraction rapidly diminishes.

This fatigability is not confined to the motor system alone. We will later see how it involves the great automatic mechanisms also, such as respiration, circulation and thermogenesis. Bourgeois suggests that the emotional depression and lessening of intellectual vigor that occur in some cases of the disease are comparable phenomena.

It is interesting to note that this state of fatigability has been produced by physiologists in studying intoxication by veratrine which is capable of producing analogous states.

2. Ocular disturbances. These are rarely if ever lacking. Often they are the first symptoms

*Read before the Providence Medical Association, December 2, 1929.

and may appear a long time before any other disorders. In some cases the ocular symptoms comprise the sole ones from beginning to end of the disease. Spiller has reported three such cases. These ocular disturbances may consist of: (a), ptosis; (b), disturbances of other external muscles of the eye; (c), disturbances of the internal musculature; (d), disorders of the visual field and of visual acuity.

Ptosis is one of the most important symptoms; it often appears long before other ones and shows certain characteristic features. At first it is irregular and unequal in degree, more marked on one side than the other. It may vary in the course of a single day. It increases with fatigue and reaches its maximum in the evening. It gradually becomes more marked as the disease progresses in evolution. In the advanced cases the ptosis may be complete and not be relieved by rest, such as a night's sleep. As a result of the ptosis the patient often presents a characteristic position of the head, his chin raised and his head thrown back in order to see ahead of him.

In addition to the levator palpebrae superioris other external muscles of the eye may be affected. Their weakness determines numerous symptoms such as diplopia, external or internal strabismus, difficulty of convergence, etc. A characteristic of these ocular paralyses is that they are fleeting and accentuated by fatigue. A complete external ophthalmoplegia (usually temporary) may appear. Nystagmus may occur on extreme lateral direction of vision. A paralysis of convergence exists at times but never as paralysis of an isolated function since in all such cases there is a limitation of excursion of the ball in lateral vision. The diplopia is dependent upon exhaustion of the external muscles and varies from day to day or even in the course of the same day. We see thus that all these ocular paralyses are, in the early stages of the disease, quite variable both in intensity and location. This is a diagnostic feature of considerable importance.

The weakness of the internal musculature of the eye in myasthenia has aroused much discussion, but undoubtedly exists occasionally and, of course, consists of exhaustion of the power of accommodation. A weakness of the sphincter of the iris is in part responsible.

The ptosis naturally leads to a narrowing of the visual field. The eye ground and optic nerve are never affected.

3. Disturbances of facial expression, phonation and deglutition. Disturbances in the facies are exceeded in frequency only by those of the eyes. While a paresis or transient paresis may be limited to a single muscle yet one most frequently sees a sort of atony and lack of expression of the physiognomy produced by a global weakness of the muscles of expression. This association of the weakness of the face and of the external musculature of the eyes produces a characteristic facies in myasthenia. In some cases the facial diplegia associated with the weakness of the orbicular and zygomatic muscles gives rise to what is described as a nasal smile or grin. The weakness of the masseters, buccinators and pterygoids may permit the mouth to remain open. Because of the ptosis and in order to compensate for the drooping of the eyelids the patient may contract his frontalis muscle, thus elevating his eyebrows and wrinkling his forehead. This imparts an expression of astonishment and mild stupidity while the atony of the lower part of the face and in particular the sagging of the angles of the mouth accentuate the naso-cheek folds and give the appearance of a painful contraction of the facies which is increased by fatigue.

Disturbances of phonation are almost as frequent as those of expression; the voice at first normal soon becomes hesitating, less and less distinct and may end in a complete aphonia. This may be illustrated by asking the patient to count. After a time he speaks more and more slowly, pronounces the numbers badly and finally stops, exhausted by the effort. This disturbance of speech may be the first symptom and attract attention by the way the patient tends increasingly to "talk through his nose" as he reads aloud. Laryngoscopic examination reveals a weakness or an immobility of the vocal cords.

Disturbances of deglutition depend upon the muscles of mastication, of the musculature of the tongue and of the soft palate. At the beginning of the meal the patient may eat without difficulty, then mastication becomes more and more painful, and increasingly long pauses are necessary. The muscles of the soft palate fatigue easily and after the patient has swallowed several times, liquids begin to flow back through the nose.

4. Other neuro-muscular disorders. Slight palsies and paralyses are frequent. On close examination, however, it will usually be found that

they are in fact extreme degrees of fatigue which has become so intense that it persists permanently, and the muscle is immediately exhausted on the slightest attempt at contraction. These paralyses appear most frequently in the extremities but may occur elsewhere. The muscles of the neck may, for example, be affected and cause the head to fall forward so that the patient is obliged to support it with his hands. The muscles of the trunk may become so feeble that they will not support the body.

There has been much discussion concerning the occurrence of muscular atrophy in myasthenia. The best opinion now states that a true atrophy (amyotrophic) does not occur but rather that one deals with a general wasting away such as may be seen in any disease as serious as myasthenia. Muscular tonus is usually normal and it is doubtful if fibrillary tremors ever occur.

Sensory disturbances are rare and if they occur it is in the early part of the disease and are subjective in nature consisting of pains and paresthesias. Myasthenia is primarily a disease of the motor apparatus.

The tendon reflexes are usually normal but the fatigability of the tendon reflex is emphasized by some writers. Some have reported the loss of the soft palate reflex but it is difficult to say whether it was a question of asthenia of the palatine and pharyngeal muscles or a disturbance of the innervation of the pharynx and soft palate.

Disturbances of the spinal fluid have never been reported.

5. Disorders of viscera and body fluids. Visceral disturbances: These may be classified as cardio-vascular, respiratory and digestive.

The pulse is usually rapid and suffers further increase with fatigue in exercise. The arterial tension is often low but it never reaches the extreme seen in adrenal insufficiency. The electrocardiographic curve is not altered.

The respiratory disorders are characterized by paroxysms of suffocation which come on suddenly and constitute the most alarming aspects of the disease and in not a few cases lead to the death of the patient. The paroxysmal dyspnea usually comes on suddenly, rapidly reaches its height and may last from several minutes to some hours. The patient suddenly feels a sense of thoracic constriction, the respiration becomes rapid and superficial. He has a feeling of not having strength enough to force air into the thorax. Suddenly a glairy, very adherent and abundant mucus appears, obstructing the isthmus of the pharynx. The sense of fatigue reaches its maximum, the patient feels himself asphyxiated and yet he cannot remove the viscid mucus. One feels like performing a treacheotomy but it would be without result. These paroxysms thus lead to death in a certain number of cases. The suddenness and severity of these paroxysms suggest failure of the respiratory centre but as to this there is nothing definite. Fits of coughing may result from the entrance of food into the respiratory passages. Even at rest the respiration is apt to be abdominal, superficial and hastened by fatigue.

Besides the difficulties with deglutition the chief gastro-intestinal trouble is constipation due to a fatigability or paralysis of the intestinal musculature.

Various disturbances in the blood picture have been reported, the most frequent departure from normal being a polycythaemia and eosinophilia.

The variations of basal metabolism do not exceed the physiological limits. Disturbances in the amount of calcium have been reported and are stressed by some writers, but Bourgeois, who has conducted the latest and most exhaustive investigations in myasthenia, calls attention to the extreme variability of the reports and expresses the opinion that all quantitative analyses of calcium in the blood are open to suspicion and that no important conclusions can be drawn from the reports. Hydrogen ion and alkaline reserve are unchanged. Estimates of the elimination of creatinine, which is known to play an important rôle in muscle metabolism, has given such variable results as not to warrant any conclusions. Some cases have shown vasomotor and trophic phenomena but they are infrequent and inconstant.

6. Endocrine and sympathetic disturbances. Disturbances in the endocrine system are variable both in frequency and nature. Some writers have emphasized tumors of the thymus but Bourgeois who took radiograms of eleven cases he studied, failed even to find a shadow. A study of the vago-sympathetic system by the usual methods has furnished but little information and nothing that will serve as a theory of pathogenesis.

Course: Myasthenia has no well defined evo-

lution but most frequently one observes a slow and progressive course. The ocular symptoms usually appear first but occasionally the disease begins in the extremities, the eyes and face becoming involved later. The progress of the disease is usually by exacerbations. Long periods of spontaneous remissions are possible, not infrequently to be followed by relapses even though the patient may have appeared to be in complete health for years. Infections are apt to cause relapses, sometimes fatal ones. Widal and Marinesco reported a case that died in fourteen days after first appearance of symptoms. Dorendorf's case died in nineteen days. On the other hand, cases have been followed for eighteen years.

Diagnosis: The diagnosis of myasthenia gravis is comparatively easy if one thinks of the condition.

In the beginning the ocular paralyses, when isolated, may make one think of syphilis, encephalitis or progressive nuclear ophthalmoplegia. In myasthenia, however, the clinical picture of that disease gradually completes itself, and the characteristic feature of variability of the symptoms from day to day or even in the same day is another characteristic.

Polyneuritis may present features suggesting myasthenia. The diagnosis rests upon the presence of subjective or objective disturbances of sensation, some degree of muscular atrophy, changes in reflexes and electrical reactions, and finally upon the fixed character of the symptoms which contrast with the variability of symptoms seen in myasthenia.

Acute motor neuritis or poliomyelitis of an ascending type with bulbar involvement may be difficult to differentiate from the acute form of myasthenia with respiratory embarrassment.

All other diseases accompanied by bulbar symptoms must of course be differentiated from myasthenia gravis, sometimes known as ascending bulbar paralysis. True bulbar palsy rarely involves the upper part of the face or the ocular muscles and then only in advanced stages of the disease. The presence of atrophy and fibrillary tremors will exclude myasthenia. In pseudobulbar palsy the upper face is not involved, the ocular muscles escape, while the history of repeated apopletic strokes makes the diagnosis easy. Amyotrophic lateral sclerosis may be excluded by the absence of ocular involvement and the presence of atrophy, fibrillary tremors and exaggerated reflexes.

The differential diagnosis from the infantile or facial form of progressive muscular dystrophy may at times not be easy. The dystrophies usually begin at an earlier age. Even in the facial form of dystrophy the proximal portions of the limbs and neighboring trunk are usually atrophied. There are very few cases of dystrophy on record in which the ocular muscles were involved. Duchenne believed that the facial form never begins after a person reaches adult life. The facies with its "tapir mouth" differs in dystrophy from that already described in myasthenia. The muscles of deglutition are not involved in muscular dystrophy.

The differentiation from epidemic encephalitis is sometimes difficult when at the beginning of that disease the ocular symptoms are the only disturbances.

Because of the physical weakness in the two diseases, insufficiency of the adrenals may at times be confused with myasthenia. In the former disease the weakness is constant and independent of movement; in myasthenia the weakness develops after exercise. In myasthenia the disease often predominates in areas supplied by the cranial nerves, whereas in adrenal disease the distribution is more diffuse.

Pathological Anatomy:

1. Nervous system: There do not exist in myasthenia specific nervous lesions capable of being revealed by our present methods of examination. This is not to say that the nervous system plays no rôle but only that the disease does not produce fixed, extensive, permanent and systematized lesions.

2. Muscular lesions: In 86% of cases lesions of extremely variable intensity are found. These changes were first described by Buzzard who gave them the name of lymphorrhagia. This name was chosen because he found foci in the muscles made up of cells which cannot be distinguished from lymphocytes either by their shape or by the character of their nuclei and because these lesions infiltrate the tissues in the same manner as do red cells in case of capillary haemorrhage without inflammatory or other distinct change in the structure of the surrounding tissue. The interpretation of this lesion which has occasionally

been described, too, in other organs and in exophthalmic goitre and in amyotrophic lateral sclerosis, is uncertain. The intensity of its process bears no relation to the severity of the myasthenia.

Recent investigations fail to disclose any changes in the intramuscular terminations of the nerves. Masses of fine pigmentary granules were found filling some fibres and between the fibres were non-staining masses believed to represent products of pigmentary degeneration of muscle. There is no way of telling whether these changes, which it must be remembered are not invariable, are primary or secondary.

Finally, various but inconstant disturbances of the thymus are reported. Their importance is unknown.

Electrophysiology of myasthenia: In 1895, Jolly described what he called the myasthenic reaction, a modification of electric reaction that he believed to be characteristic and specific of myasthenia. Essentially this reaction consists in an increasing rise of the threshold of stimulation with progressive diminution of the height of the contraction as one repeats the stimulations. Stated differently, if a rapidly interrupted current is applied to normal muscle no change in the muscular contraction is noted even though the current is continued over an hour. In a myasthenic muscle such a current at first produces a normal contraction but the contraction rapidly decreases and then disappears. After a brief rest, the muscle may again be made to contract, although for a very brief period.

The nature of this myasthenic reaction is a matter of dispute. Bourgeois at the Salpetriere after extensive experiments in the electrophysiology of the disease, states in a recent monograph that the myasthenic reaction is simply a fatigue reaction and is found in many states of fatigue that have nothing to do with myasthenia. He found, too, that the chronaxie, or time necessary for an electric current to put a muscle into action, shows the same departure from normal both in myasthenia and in conditions of fatigue. On the other hand, Stanley Cobb in an article in "Brain" published in December, 1928, antedating somewhat the monograph by Bourgeois, claims that the exhaustion of the muscle in myasthenia gravis is electro-myographically quite different from the fatigue of normal muscle. He claims that the absence of adequate action current indicates the absence of adequate contractability and not excessive fatigue. All electromyographic evidence indicates that the exhaustion is due to causes peripheral to the ventral horn cell and probably in the muscle cell itself.

Theories as to pathogensis: Many theories have been advanced to explain this unusual disease. Briefly there are nervous theories, muscular theories, endocrine theories, theories of visceral origin and finally a vegetative or suprarenal-vegetative theory.

Clinically myasthenia with its serious paroxysmal accidents suggests a disease of the nervous system but post-mortem findings are not consistent with such a suggestion. Even though there is a terminal bulbar weakness it is no proof that the essential lesion is primarily or essentially bulbar.

As for the muscular theory, we know from an acquaintance with the physiology of muscle that when a muscle is intoxicated by a product it fatigues more easily than normal muscle, also, on the other hand that muscular fatigue causes in the muscle the elaboration of toxic products which for a time inhibit motor function. As to the possible relation of such processes to myasthenia the following questions arise: From what sources in myasthenia could products arise which could render muscle fibres more fatigable? What are the organs an alteration of which may prevent the neutralization or elimination of muscular toxins, the products of fatigue, which interfere with the muscle in its utilization of its reserves?

Such questions suggest consideration of a possible pathogenic rôle of the endocrine glands or of the neuro-vegetative system. In this connection, one must remember that the establishment of either clinical or anatomical disturbances of the endocrines in myasthenia is not constant. Bourgeois, whom I have so often quoted in this paper, did not find important glandular troubles in any of his cases. Lesions of the endocrines doubtless exist in some cases but are so inconstant that they must be looked upon as perhaps predisposing but not the sole cause of myasthenia.

Marinesco, of Bucharest, has published, both in Roumania and in France, the results of numerous experimental investigations which have led him to believe that vegetative disturbances constitute the basis of myasthenia and that as a re-

sult of these vegetative disturbances there occurs a dysfunction of the endocrines, particularly of the suprarenal. The details of his observations are unfortunately too long to give here.

As a whole his observations are doubtless correct but many other investigators cannot believe that the fleeting and inconstant phenomena manifested in myasthenia by the sympathetic system can be the ultimate cause of an affection so severe, distinct and fixed as is myasthenia.

Finally, let us attempt to synthesize the theories as to pathogenesis. Before doing so the question ought to be decided as to whether myasthenia gravis is a distinct disease or whether myasthenic syndromes arise from different causes. Myasthenic symptoms doubtless occur in many infections and intoxications but apart from these there appears to be a definite disease with a constant clinical picture and fairly definite evolution. From a clinical point of view the disease manifests itself characteristically by a fatigability of extremely variable intensity, a fatigability appearing on effort and relieved by rest. The absence of changes in the chronaxie of the nerve, while that of the muscle is changed, shows that the phenomena of fatigue arise in the muscle itself. This agrees with the frequency of anatomical changes noted in the muscle and with the vasomotor changes in the muscle observed by Marinesco. This, however, does not mean that myasthenia is primarily and exclusively a disease of the muscle.

The variability of the symptoms and the fact that the phenomena or fatigue develop not only in the muscles which are in action, but also in those at a distance are arguments that lead one to suppose that when muscular effort occurs a state of intoxication, is developed or aggravated and that the toxic products produced by this muscular effort are diffused throughout the organism by the body fluids.

It is not possible to account for the nervous lesions found at autopsy but the clincal picture seems to indicate that certain accidents in myasthenia and particularly the serious terminal respiratory ones are due to a bulbar weakness. The hypothesis of a toxic origin of myasthenia agrees with that of bulbar disturbances and the apparent absence of definite system changes.

There is no doubt that endocrine lesions are relatively frequent in myasthenia. This fact has often been used as an argument that their role in the disease is not incidental only. Physiology teaches us that one function of the endocrines is to neutralize the products of fatigue. Doubtless unusual demands must be put upon this function in myasthenia. Thus is explained the hyperfunctioning of certain glands that seem to be working at capacity, or on the other hand the insufficiency of other glands which appear exhausted. In this way may be explained the diversity of glandular lesions in an affection which must make the maximum demands upon the endocrines to exercise a function that they all possess to some degree. It seems then that a disturbance or inadequacy of endocrine function may be a predisposing factor in myasthenia, such changes rendering the endocrines inadequate to perform their usual function of neutralizing fatigue toxins.

If one admits a toxic origin of myasthenia it remains to locate the origin of the poison. Is it a case of endogenous or of exogenous intoxication? Are the toxins secreted by a particular virus? What is the seat of the toxic agent? What is its mode of action? Investigations on the toxicity of the urine, inoculations with blood serum and with the cerebro-spinal fluid have been made but with practically no results.

Treatment: A correct evaluation of the results of treatment is difficult. In the first place myasthenia is a disease that often shows spontaneous improvement; secondly, patients who because of chronic disease are prevented from social activity are apt to claim beneficial results from any new treatment.

The most severe cases must be cared for in bed. To prevent fatigue from mastication, to avoid the accidents of deglutition and to avert, if possible, the paroxysms of respiratory distress, the patient should be fed small amounts frequently and then by spoon.

Physical agents like massage, electricity and exercise should naturally be avoided. Radiotherapy of the thymus has been tried with alleged benefit in a few cases, but some neurologists do not consider it free from danger.

Arsenic, phosphorus, quinine and iron have long been used. Strychnine should theoretically be avoided although benefit has been reported from the use of very large doses.

The best results, however, have been secured by the use of suprarenal extract. In this connection it is interesting to note that numerous experiments, particularly on the frog, have shown that injections of the whole suprarenal gland have an undoubted action upon fatigue, that is, it permits functional recuperation in a fatigued muscle much more rapidly than is normally possible. The question arises as to what part of the gland produces this result. Is it due to adrenalin produced by the medullary substance, or to the cortical substance? Physiologists do not agree. Clinical therapeutic experience, however, shows that adrenalin is nearly or quite without result in myasthenia while the whole gland has a remarkably effective action, and in some cases, an exceeding prompt beneficial effect.

In myasthenia suprarenal extract gives results that can be obtained by no other endocrine therapy. It would seem, therefore, to possess a specific action. Is this action purely vasomotor or does the extract have a direct action upon muscular metabolism? The work of Feriera tends to show that it is due to vaso-dilatation, a peripheral phenomenon. The rapidity of action of suprarenal extract would be in favor of this theory but the prolonged action that results seems more to indicate that it acts in the capacity of an antitoxin. Recent experimentation, too, seems to show that in myasthenia suprarenal extract acts much more by a biological process whereby the products of muscular activity are rendered inert than by a simple stimulation of vasomotor nerves. The extract is preferably given hypodermically in doses of 1½ grains. The same results cannot be secured by adrenalin. While it is agreed that this treatment offers more than any other drug or glandular therapy undesirable results have at times followed. These symptoms were pallor, tendency to syncope and an immediate increase in the fatigue phenomena.

* * * *

Patient, M. C., 72 years of age was committed to the State Hospital for Mental Diseases, June 13, 1929, because for a period of 8 to 10 years he had caused much annoyance to his family because of exposing himself; finally his behavior in this respect became intolerable, the neighbors complained and he was committed.

The family history is negative except for two interesting and significant facts. One is that his father developed bilateral ptosis at uncertain age, but apparently after mid-life. The father also had difficulty with deglutition. The other fact of interest is that a sister, now 76 years of age, began to have double ptosis at about 60.

The patient was born in Canada and came to the United States when 33 years of age. He claims that except for the present complaint he has always been well.

About 17 years ago the patient began to have difficulty in swallowing anything except soft food and liquids. At the Hospital it is noted he never attempts to eat any meat and that he soaks his bread in his tea or coffee.

For several years, probably six or seven, he has been troubled with regurgitation of liquids through his nose. This he says is worse with cold liquids, a condition observed in other instances of the disease.

About fifteen years ago the patient began to suffer from bilateral ptosis. This was evidently of insidious onset as he says, "It came on little by little. At first I could force my eyes open." The present degree of ptosis has apparently existed for seven to ten years. The only other ocular symptom, but a very significant one, is that the patient complains that after reading for half an hour he is troubled with diplopia.

The patient was a carpenter by occupation and followed this trade without incident until after the onset of his throat and ocular symptoms. He then began to notice that he tired more easily. The easy fatigability increased until he become no longer able to compete successfully with others of his trade. He would be obliged to stop work and go home in the middle of the afternoon. Finally ten years ago he was obliged to stop work entirely. He complains that for several years his arms and legs have been weaker, "some days weaker than others." He has not experienced any difficulty in breathing.

The physical examination reveals little of significance except the neurological examination. He does, however, show considerable arteriosclerosis and his blood pressure is 180/100. The Wassermann reaction of the blood was negative as was that of the spinal fluid which showed but one cell, no globulin and a negative colloidal gold reaction. Urine was negative except for a faint trace of albumin and a few pus cells. The

number of red and white blood cells was normal but the hemoglobin was somewhat low—68%. The differential count was entirely within normal limits. The blood sugar was 114 mgs., the N. P. N. 64½ on admission, subsequently falling to 26 mgs. X-ray examination did not show any evidence of persistence or tumors of the thymus.

The patient's appearance is quite striking. One at once observes the bilateral ptosis. While the globe of the eye is not completely obscured the pupil is sufficiently covered so that there is considerable interference with vision. In an attempt to raise his upper lids, which can no longer be elevated by the levator palpebrae superioris, the patient contracts his occipito-frontalis thereby pulling up his eyebrows and throwing the skin of his forehead into folds. As vision directly ahead is still interfered with he often carries his head thrown back in a still further attempt to extend his visual field upward. The contraction of the orbicularis palpebrarum is vigorous and he can close his lids firmly.

The pupils are equal, round and react well to light and convergence. There is no strabismus. At times slight nystagmoid movements are observed on extreme lateral direction of vision. I am indebted to Dr. Jeffrey J. Walsh, visiting ophthalmologist to the State Hospital, for examination of the eye grounds. Dr. Walsh reports the eye grounds negative except for the evidence of a small, very old haemorrhage.

Smell appears to be unimpaired. The patient does not complain of weakness of his masseters or variability of their strength. I have, however, had him bite on objects toward the end of his meal and again several hours after eating and the bite appeared distinctly weaker after he had been chewing for a time.

The facial expression appears somewhat immobile and lacks tonus and expression. Hearing is normal, taste is unimpaired. The tongue shows no atrophy or fibrillary tremors and its movements are free and vigorous. Irritation of the soft palate produces no reflex response, but stimulation of the anterior pillars will produce contraction of the muscles in them. Biceps, triceps, patellar and Achilles jerks are present but not lively. There is no clonus. Sensation is not disturbed.

Speech is of a characteristic bulbar type due to weakness of the muscles of the throat, and is of a nasal, mumbling nature. Some patients easily become exhausted on attempting to read aloud and first show the tendency to nasal speech on trying to read in this way. Our patient on being asked to count rapidly aloud to 100 spoke a little less vigorously as he approached that figure but was not exhausted.

All summer the patient acted as a guide for a blind man about the grounds. Recently he has complained that he is losing strength and has largely given up walking about the grounds.

We see, therefore, that this patient presents certain interesting features. I have been unable to find in the literature any case in which there has been an equal degree of familial occurrence of the disease. Another interesting fact is the long continuation of the disease. While certain cases apparently recover, or at least remain well until occurrence of a subsequent infection, yet the disease in this patient has slowly but uninterruptedly progressed for a period of at least seventeen years. The disease, too, has been largely limited to the extra-ocular muscles and those of mastication and of deglutition. In addition to the fact that the disease has continued longer than usual, its onset was at a more advanced age than is ordinarily the case.

NOTICE

The second issue of "The Hebrew Physician," (Harofeh Hoibri), the only Hebrew Medical Journal published outside of Palestine, has just made its appearance.

This Journal is under the editorship of Dr. Moses Einhorn and Dr. L. M. Herbert. It consists of 180 pages, and contains numerous articles on general medical subjects, including a copy of the manuscript on "Hemorrhoids," by Shlomo Eben Ayub of Badrash, France, (1265 A.D.). A special section is also devoted to new Hebrew medical terminology.

All physicians who are interested in this journal, are requested to communicate with The Hebrew Physician, 983 Park Avenue, New York City.

THE RHODE ISLAND MEDICAL JOURNAL

Owned and Published by the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee, 106 Francis Street

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The R. I. Medico-Legal Society—Last Thursday—January, April, June and October. Henry M. Boss, Jr., President; Dr. Jacob S. Kelley, Secretary-Treasurer.

EDITORIALS

DENATURANS

The problem of "Denaturing" commercial alcohol, now so very much under the public eye, has never received the attention it deserves. Some time ago there were seven different formulae use for denaturing purposes and when one sought alcohol he did not know which one was used. Now alcohol is an invaluable fuel and chemical and it is to be understood that the Government campaign of supposed prohibition is one against drunkenness and its associated evils and not one against business, science and industry. Alcohol is one of the best fuels known, it has high antiseptic properties and is used to a very great extent in the arts and sciences. With such widely diversified uses it is of great importance that the purchaser know exactly what he is getting when he buys denatured alcohol. The Government has no more right to sell adulterated alcohol than any merchant has to sell any "doctored" or changed commodity. It has no right to incorporate in a chemical any substance that may injure machinery or participate in any chemical reaction that may take place in just and honest investiga-

tion. Therefore we say that if we buy a gallon of alcohol that has been issued by the Government or any business house or firm we have a right to know just what and how much foreign matter has been added to the fluid to make it fit, for use in the arts if not in the artists. It might appear that denaturants need not necessarily be lethal. It may be that a good brisk attack of gastro-intestinal symptoms would convince the user that he was using a chemical for beverage purposes, thereby preventing a repetition of the offense to the Government and an insult to his physique. We wonder if the all-wise Government has considered such denaturants; at all events the present state of this aspect of prohibition is far from satisfactory nor is it in keeping with the present scientific trend of the industrial arts.

And by the same tokens must we review those causes which cause a charge of $6.00 a gallon for pure medicinal alcohol for a chemical that can be made and sold at a profit for forty cents. It is a sad criterion upon our civilization that so useful a substance as alcohol must be so greatly inhibited in its usefulness and that the sick must be penalized by the few who divert it from its proper uses for the sake of a thrill, bun or jag as their reaction is described.

RESPIRATION FERMENT

In E. E. Free's list of the ten greatest living scientists, the name of Dr. Otto Warburg of Berlin is included because of his researches into the relations of oxygen to living cells. Under modern living conditions, especially in our cities, with diminished oxygen content and constantly increasing percentages of carbon monoxide in the air which is available for respiration, this subject becomes daily of increasing importance. Oxygen is taken up by the blood hemoglobin and distributed to the cells in different parts of the body simply enough. But in order that the oxygen may be taken up by the cells and take part in the process of metabolism, some intermediate agent is required. This agent is the respiration ferment.

Ferments are necessary for effecting chemical changes in living matter. As no ferment has yet been isolated, their chemical composition is not exactly known. From Dr. Warburg's studies the characteristics of the respiration ferment are well outlined. In the presence of the respiration ferment, atmospheric oxygen becomes available for chemical combination in living cells. When a considerable percentage of carbon monoxide is present in the blood, it is taken up by the respiration ferment, blocking its action so that it is unable to continue its catalytic effect between oxygen and the body cells. Cell respiration then ceases.

This effect may be reversed by introducing into the blood plasma an increased percentage of oxygen or by exposing the tissues to light. The intensity of light required to effect the distribution of the respiratory ferment is only one ten-thousandth the intensity of sunlight. If the respiration of cells is inhibited by exposure to carbon monoxide and the cells are then exposed to light of different wave lengths, the cell respiration rises to different heights according to the wave length employed. The effect of ultra-violet rays is very small. The blue rays have the greatest effect. Green has a smaller effect and yellow still less. The respiration ferment absorbs light of different wave lengths to different degrees and is most affected by blue rays.

The respiration ferment unites with oxygen and with carbon monoxide reversibly, the reaction depending on the percentage of oxygen and of carbon monoxide present. The combination of carbon monoxide with the respiration ferment is sensitive to light, especially to the blue rays. The combination of oxygen with the respiration ferment is unaffected by light. Such is the nature of the researches which led Free to choose Dr. Warburg to represent the medical profession in his list of the ten greatest living scientists.

RHODE ISLAND HOSPITAL

Clinical-pathologic Conference

Case reported by Dr. Ferguson.

M. C., age 45, female, white, married. Admitted April 28, 1929.

C. C.: Pain all over the abdomen and flanks.

P. I.: For years the patient has had attacks of indigestion. These consist of gas, belching and gastric pain following meals. Soda bicarbonate gives some relief. On the morning before admission while sitting at the table eating she sud-

denly got up and complained of being very sick. She lay down on a couch and began to vomit. She seemed very ill and complained of much pain in the abdomen. At times she was irrational. Continued in this condition to admittance.

P. H.: Because of the condition of the patient no past history was obtained.

Physical Examination

Well developed and somewhat obese white woman lying in bed and groaning as if in severe pain. Temperature 102. Pulse 120.

Head, eyes, ears: Ext. negative.

Mouth and Throat: Tongue dry and heavily coated with brownish film. The pharynx deeply injected.

Heart: Not enlarged. Apex beat felt in fifth interspace. Sounds regular, weak and very rapid. Pulse 120.

Lungs: There is a questionable dullness in the right base posteriorly. On auscultation there is a friction rub in the right axilla.

Abdomen: Protuberant. Generalized rigidity and tenderness. No masses felt. Solid organs not palpable.

Extremities: Negative.

Vaginal: A pedunculated soft mass protruding from external os.

Laboratory Findings

Urine: Acid. Albumen 1+. No sugar. A few pus cells.

Blood: W. B. C. 15,700. Polys 85%. Lymph. 14%. Urea N. 43. Creatine 1.7. Glucose 95.

A provisional diagnosis or pneumonia was made and the patient was referred to the medical service. The medical service failed to substantiate the diagnosis of pneumonia but felt that there was an acute abdominal condition.

Because of the patient's poor general condition operation was withheld. She failed rapidly. The abdominal tenderness and rigidity persisted. She became very noisy and irrational. Death occurred at 12 noon, April 30.

Autopsy obtained.

Discussion

Dr. Ferguson pointed out that the history though meagre indicates that there was some chronic disease of the abdomen. It seemed logical to conclude that there was a direct connection between the past symptoms and the present acute condition. Of the many possibilities he placed first ruptured gall bladder followed by perforated gastric ulcer and ruptured appendix. In the discussion which followed the consensus of opinion seemed to favor perforated gastric ulcer. An additional diagnosis or pancreatitis was also offered.

Demonstration of Postmortem Material
(Dr. Clarke)

On opening the peritoneal cavity the loops of intestine were found matted together and covered over with a thick layer of fibrin. This fibrin extended up over the surface of the liver. In the pelvis was a thin puriform material.

A careful search was made for the point of origin of this acute inflammation. Here is the appendix. It is fibrosed and surrounded by old fibrous adhesions. There is no acute appendicitis. There is no ulcer or other lesion in the stomach. The gall bladder wall is thicker and whiter than normal. Within it are two small stones. The mucosa presents the so-called strawberry appearance. There is nothing acute here. The pelvic organs too are negative. In the fundus of the uterus is a large encapsulated smooth muscle tumor. A second tumor measuring 6 cm. in diameter is attached to the endometrial surface by a long pedicle which extends out through the external os so that the tumor hangs in the vagina.

The pleural surfaces of the right chest are covered by thick layers of fibrin. There is no pneumonia of the underlying lung.

All parenchymatous organs show congestion and cloudy swelling. A pure culture of pneumococcus was obtained from the peritoneal and pleural exudates.

Pathologic Diagnosis

Fibrinous peritonitis (pneumococcic).
Fibrinous pleurisy (pneumococcic).
Chronic cholecystitis.
Cholelithiasis.
Chronic appendicitis.
Leiomyomata of uterus.

Case reported by Dr. Westcott.

J. O.: Age 25, male, white, single. Admitted April 9, 1929.

C. C.: Pain in left ear and shortness of breath.

P. I.: During past three to four years the feet and ankles would swell when the patient was drinking. Has drunk considerably during this time. He was short of breath on exertion but this disappeared when he cut down on cigarettes. He was fairly well until last September, when he began to have a chill each night. After that he began to have edema of the ankles and shortness of breath. His physician told him he had heart trouble. About six weeks ago he was obliged to go to bed where he has remained until present time. Two days before admission developed pain

(Continued on page XXIV)